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EXAMINER

MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 05/06/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/446,109

Applicant(s)

FAIRLIE ET AL.

Examiner

Abdel A. Mohamed

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7. 6) ☐ Other:

Art Unit: 1653

DETAILED ACTION

ACKNOWLEDGMENT FOR PRIORITY, PRELIMINARY AMENDMENTS, IDS, SEQUENCE LISTING, RESPONSE TO RESTRICTION REQUIREMENT, STATUS OF THE APPLICATION AND CLAIMS

1. This application is filed under 35 U.S.C. 371 on 4/21/00 having a filing date of 6/25/98 of PCT/AU98/00490. Acknowledgment is made of Applicant's claim for priority based on Australian Application No. PO 7550 having a filing date of 6/25/97. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The preliminary amendments filed 4/21/00, 5/3/01 and 2/4/02, respectively, the information disclosure statement (IDS) and Form PTO-1449 filed 5/19/00, the sequence listing filed 9/19/01 and the response to the restriction requirement filed 2/4/02 are acknowledged, entered and considered. In view of Applicant's request claims 1-5, 7-9, 13-14, 17-18 and 20-21 have been amended and claims 24-32 have been canceled. Thus, claims 1-23 are now pending in the application.

ELECTION WITH TRAVERSE

2. Applicant's election with traverse of compounds of Structure II as a single disclosed species in Paper No. 15 is acknowledged. The traversal is on the ground(s) that this application is a 371 of PCT/AU98/00490, filed 6/25/98, and is properly subject to restriction only under the PCT Rules. As noted in MPEP § 1895.01(D), restriction practice under 35 U.S.C. § 121, as it

Art Unit: 1653

applies to national application submitted under 35 U.S.C. § 111(a), is not applicable to a national stage application such as this one is persuasive. Thus, based on the PCT administrative instructions in MPEP, Annex B, Part 1, which provide direction on restriction practice under the PCT Rules, the election of species requirement was improper. Hence, the election of species requirement is withdrawn.

ABSTRACT MISSING

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

CLAIMS REJECTION-35 U.S.C. 112^{1st} PARAGRAPH.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical formulations of cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof, does not reasonably provide enablement for pharmaceutical

Art Unit: 1653

formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared *per* the factors indicated in the decision *In re Wands*, 8 USPQ2 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

- 1) the nature of the invention;
- 2) the breadth of the claims;
- 3) the predictability or unpredictability of the art;
- 4) the amount of direction or guidance presented;
- 5) the presence or absence of working examples;

Art Unit: 1653

- 6) the quantity of experimentation necessary;
- 7) the state of the prior art; and
- 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and state of the prior art in the assessment of undue experimentation.

- 1) the nature of the invention;

The instantly claimed invention is directed to a pharmaceutical formulation comprising C5a antagonists or agonists with the dimensions defined by co-ordinates A, B, C and D and a method for treatment of a pathological condition mediated by a G protein-coupled receptor in patients by administering therapeutically effective amount of said formulation thereof.

- 2) the breadth of the claims;

The scope of the claims include pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis,

Art Unit: 1653

atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification does not disclose one reasonable method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. The specification lacks guidance/direction as to how to employ a pharmaceutical preparation useful for treatment of a pathological condition mediated by a G protein-receptor by administering to a patient an effective amount of a compound according to claim 1 in the manner claimed in claims 21-23.

Further, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

3) the predictability or unpredictability of the art;

As acknowledged by Applicant on British Journal of Pharmacology, Vol. 128, pp. 1461-1466, 1999 (Applicants own work because out of 9 authors, 4 of them are the inventors of the instant application), the reference shows the pharmaceutical characterization of antagonists of the C5a receptor. On page 1461, right column, the reference states that until recently, no potent or

Art Unit: 1653

selective small molecule antagonists have been available to evaluate therapeutic effects of blocking C5aRs. Although, C5aRs antagonists are now available for testing and further development, to date, no studies have reported on either the pharmacological nature of the antagonism or on their activities on cells other than PMNs. Further, on the abstract, the reference summarizes the result by stating that these antagonists are insurmountable in nature against C5a for C5aR on at least two human cell types, and the differences in relative receptor binding affinities and antagonistic potencies against C5a are consistent with differences in receptors within these cell types. The nature of these differences is yet to be elucidated, and concludes on page 1465 by stating that the results of the present study indicate the feasibility of such a notion. Thus, clearly showing the unpredictable nature of compounds in the method of treatment claimed.

4) the amount of direction or guidance presented;

The specification teaches pharmaceutical formulations comprising cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof as shown in Examples 1-8, Figures 2-10 and Tables 3-4. Example 1 and Table 4 teach synthesis of cyclic peptide, and Figures 2-4 and 7, Table 3 and Example 2 demonstrate NMR structure determination of cyclic antagonists. Figures 5-6 and Examples 3-6 show *in vitro* receptor-binding assay. Figures 8-10 and Examples

Art Unit: 1653

7-8 describe the *in vivo* assays of anti-inflammatory activity on rats in which paw oedema is determined by administering the carrageenan compound into the air pouch and exudate is collected and the anti-inflammatory effects is assayed by differential counting of cells in the air-pouch exudate.

6) the quantity of experimentation necessary;

The claimed invention is directed to pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. However, the phrases "cyclic agonists and antagonists" and "constrained acyclic structure" are not justified by the limited exemplary disclosure of using pharmaceutical formulations comprising cyclic peptides of formulae II or IV and the linear derivatives described which are improperly incorporated by references on page 9, lines 22-37 in the instant invention. Further, there is no working example or data or evidence which shows that

Art Unit: 1653

the claimed compounds are useful as pharmaceutical formulations in the method of treatments as claimed in claims 21-23. Although, there is preparation Examples for pharmaceutical formulations as well as *in vitro* and *in vivo* assays and certain mode of administration. Nevertheless, there is no evidence in the instant specification to use or administer the pharmaceutical formulations in therapeutically effective amount as claimed, except for the mere recitation of protocols on page 19 in the instant specification contemplating the suitable dosage of the compound to be administered generally in mammals for the intended treatment of all kinds of pathological conditions mediated by a G protein-coupled receptor. Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical formulations of claim 20 in the manner claimed in claims 21-23. Hence, the only support for the claimed pharmaceutical formulations in the specification and method of treatment thereof is Applicant's supposition of the invention as recited in the protocols. Thus, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since **all kinds** of pharmaceutical formulations comprising the various compounds in a method for treatment of a pathological condition mediated by a G protein-coupled receptor, such as rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome,

Art Unit: 1653

etc. in a mammal are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which are not clearly disclosed. Hence, one of ordinary skill in the art would not be able reproduce all the aspects the claimed invention pharmaceutical formulations as well as methods for treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a affecting the pathological conditions, such as rheumatoid arthritis, ARDS, septic shock, Alzheimer's disease, ect., as encompassed in the claims would be effective and under what conditions.

7) the state of the prior art;

Thus, in view of the above and in view of the fact that the state of the prior art as discussed above, at the time the invention was made there was no pharmaceutical characterization of antagonists of the C5a receptor; and as to date (i.e 1999-date of publication of the reference), no studies have reported on either the pharmacological nature of the antagonism or on their activities on cells other than PMNs, let alone administering an effective amount of pharmaceutical formulation of the claimed compound to treat all kinds of pathological conditions mediated by a G protein-coupled receptor in the manner claimed in claims 21-23.

8) the relative skill of those skilled in the art;

Therefore, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Thus, in view of the quantity of

Art Unit: 1653

experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims; the claims are not commensurate in scope with the enabling disclosure.

Hence, in consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teachings, and guidance presented. Therefore, absent factual data to the contrary, the amount and level of experimentation needed is undue. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIM REJECTIONS-35 U.S.C. § 112^{2nd} PARAGRAPH

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 15 are indefinite in lacking clarity with respect to the structure of amino acid D as disclosed on pages 55 and 60, respectively, since the nitrogen atom bearing the R¹ substituent is divalent rather than trivalent. Appropriate correction is suggested.

Art Unit: 1653

Claim 5 is indefinite in the recitation “and comprises.....”. The term “and” is superfluous. Deletion of this term would obviate this rejection.

Claim 8 is indefinite in the recitation “Ac-phe-[lys-pro-(dCha)-trp-arg] or Ac-phe-[orn-pro-(dCha)-trp-arg]”. The sequence listing in the specification and claims must have 3 letter codes as required by 37 CFR 1.822(e) and the first letter of the sequence must be capitalized. Thus amendment of the claim to recite “Ac-Phe-[Lys-Pro-(dCha)-Trp-Arg] or Ac-Phe-[orn-Pro-(dCha)-Trp-Arg]” is suggested.

Claim 13 is indefinite and confusing in referring back to compounds in numbers in the specification because referring back to a Figure or a Table or a Number is not acceptable claim language. Such material should be incorporated within the claim language. Further, it is long standing Office practice that claims should be complete and self-contained and incorporation into claims by express reference to the specification is not permitted and should not be relied on to define the invention (*Ex parte Fressola*, Bd. Pat. Appl. & Inter., 5/11/93, p. 1608).

Claim 21 is indefinite in the recitation “.....administering an effective amount....” because it is not clear what is meant by the terms “effective amount” since no amount of compound is claimed or disclosed, and as such, the metes and bounds of the claim cannot be determined.

CITATION OF RELEVANT PRIOR ART

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Art Unit: 1653

WO 95/16033 discloses polypeptide analogues of human C5a receptor antagonists that exhibit substantially no anaphylatoxin or agonist activity, and derivatives of the analogues, and dimeric forms of the analogues or derivatives.

Sanderson et al. (U.S. Patent No. 5,696,230) describe the use of high-affinity response-selective C-terminal analogs of C5a anaphylatoxin.

Van Ostrum et al. (U.S. Patent No. 5,807,824) teach the use of C5a receptor antagonists having substantially no agonist activity.

CONCLUSION AND FUTURE CORRESPONDENCE

7. No claim is allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Art Unit: 1653

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1800

 Mohamed/AAM

May 3, 2002